REMARKS

Prior to the present amendment, claims 1-30 were pending. Applicants have amended claims 1 and 11. Accordingly claims 1-30 are currently pending.

On page 2 of the Office Action dated August 29, 2003, the examiner acknowledged receipt and entry of the Information Disclosure Statement filed on May 17, 2002 and the Supplemental Information Disclosure Statement filed July 12, 2002 and April 14, 2003. The examiner did not acknowledge consideration of international PCT publication number WO96/29315 cited in the Supplemental Disclosure Statement filed July 12, 2002. For the examiner's convenience, applicants submit herewith a copy of PTO form 1449 filed July 12, 2002 and international PCT publication number WO96/29315. Applicants respectfully request that the examiner consider international PCT publication number WO96/29315 in its entirety and to acknowledge that he has done so by initialing PTO form 1449.

In the Office Action, the examiner objected to claims 11-16 under 37 C.F.R. §1.75(c) for allegedly being of improper dependent form. The examiner states that claim 11, which depends from claim 1, has no antecedent basis for "the H_3R antagonist...."

Applicants have amended claim 11 to depend from claim 10. Therefore, "the H_3R antagonist" recited in claim 11 now has proper antecedent basis.

The examiner further stated that claims 12-16 are directed to therapeutic objectives different from the therapeutic objective of the claim from which they ultimately depend (i.e., claim 1).

Applicants respectfully disagree. In fact, the limitations recited in claims 12-16 are related to the therapeutic objective of claim 1. For example, H_3R agonists inhibit Na^+/H^+ exchanger activity (see claims 12) thereby reducing cardiac dysfunction.

Prior to the present invention, it was not known that administration of H_3R agonists reduces cardiac dysfunction in a human. Much less was it known that administration of H_3R agonists reduces cardiac dysfunction in a human by inhibiting Na^+/H^+ exchanger activity. Thus, claims 12-16 add patentable limitations to claim 1, and are, therefore, patentable independently of claim 1.

Accordingly, the objection of claims 11-16 under 37 C.F.R. §1.75(c) should be withdrawn.

Claims 1-30 were rejected under 35 U.S.C. §103(a) as allegedly obvious over Silver et al. in view of Applicants' acknowledgement at page 7, paragraph [0029] of the specification and Avery.

The claims in the present application are supported by the disclosure in U.S. provisional application serial no. 60/268,393. Therefore, the claimed invention is entitled to the benefit of the February 13, 2001 priority date of the provisional application.

The Silver et al. article was published on-line on February 20, 2001, and in print on February 27, 2001. Thus, the Silver et al. article was published after the February 13, 2001 filing date of U.S. provisional application 60/268,393. (Attached as exhibit 1 is a text version of the Silver et al. print article, obtained from "PNAS Online" indicating just above the title on the first page that the Silver et al. article was published on-line on February 20, 2001).

Therefore, the Silver et al. article does not constitute prior art.

Claims 1-30 were rejected under 35 U.S.C. §103(a) as allegedly obvious over Mackins I, Mackins II, Levi et al., Imamura et al. and Leurs et al. in view of Applicants' acknowledgement at page 7, paragraph [0029] of the specification and Avery. The rejections will be summarized, and then addressed collectively.

According to the examiner, Mackins I and II disclose that histamine 3 receptor (H_3R) agonists inhibit noradrenaline (i.e., norepinephrine) release and that H_3R agonists should be useful in the treatment of myocardial ischemia and infarction. The examiner states that the Levi et al. article indicates that negative modulation of NE release by H_3R agonists may offer a novel therapeutic approach to myocardial ischemia. The Imamura et al. article is said to disclose that histamine H_3 receptors downregulate norephinephrine exocytosis, which is markedly enhanced in early myocardial ischemia. Lastly, the Leurs et al. reference, according to the examiner, teaches that thioperamide and clobenpropit are antagonists of H_3 receptors.

Nowhere in Mackins I, Mackins II, Levi et al., Imamura et al. and Leurs et al. is there any direct evidence that administration of H_3R agonists reduces cardiac dysfunction in humans. There are, at most, ambiguous and speculative statements in these references suggesting, at best, that administration of H_3R agonists might reduce cardiac dysfunction.

For example, Mackins I and II only suggest that H_3R agonists may reduce cardiac dysfunction. The authors state on page 2539, line 1 of Mackins II the following:

> ...H_3R agonists **may have** therapeutic potential in both acute and protracted myocardial ishaemia. *(Emphasis added)*

Levi et al. also speculate that H_3R agonists may reduce cardiac dysfunction. Levi et al. state on page 827, first sentence in first full paragraph in right column the following:

> ...H_3R **might play** an important modulatory role in cardiac dysfunction. *(Emphasis added)*

Imamura et al. also hypothesize that H3R may be useful in reducing cardiac dysfunction. The authors state in the fist paragraph on page 481, the following:

> Collectively, these findings **may further** the development of novel pharmacological means to reduce reperfusion arrhythmias in the clinical setting. *(Emphasis added)*

Leurs et al. also speculate that H_3R agonists may be of therapeutic use. Leurs et al. state in the first paragraph on page 180, the following:

> Since CGRP release is elevated in humans in severe conditions such as septic shock, heart failure and acute myocardial infarction, H_3 receptor agonists **might be** of therapeutic use in these conditions. *(Citations omitted and emphasis added)*

Taking the teachings of Mackins I and II, Levi et al., Imamura et al. and Leurs et al. as a whole, a person having ordinary skill would not accept that there is a reasonable expectation of success that H_3R agonists would be effective in reducing cardiac dysfunction. As demonstrated above, these authors only hypothesize that H_3R agonists **may be** of therapeutic potential in reducing cardiac dysfunction.

Therefore, at most, it may have been obvious to try H_3R agonists for treating cardiac dysfunction. Suggestions to try, however, are not sufficient to sustain a *prima facie* case of obviousness.

In support of applicants' argument that there was no expectation of success, applicants would like to bring to the examiner's attention the article by Mazenot et al. published in *Fundam. Clin. Pharmacol.* 1999, 13:455-60. Mazenot et al. was cited in the IDS filed May 23, 2002. Mazenot et al. discloses that in a rat model, the H_3R agonist R-α-methyl-histamine failed to modulate release of norepinephrine during ischemia-reperfusion. See first paragraph in results section on page 456 and second paragraph in discussion section on page 457.

A person having ordinary skill in the art would understand from Mazenot et al. that administration of an H_3R agonist is **not** effective in reducing cardiac dysfunction. In combination with the cited references, Mazenot et al. adds to the uncertainty in the mind of a person having ordinary skill in the art regarding whether administration of an H_3R agonist would be effective in reducing cardiac dysfunction.

Thus, the disclosure of Mazenot et al. supports applicant's statement that there was no reasonable expectation that stimulation of H_3R would reduce cardiac dysfunction.

Therefore, a *prima facie* case of obviousness does not exist. At most, the prior art renders it obvious to try an H_3R agonist to reduce cardiovascular dysfunction. As already mentioned above, suggestions to try, however, are insufficient to establish a *prima facie* case of obviousness.

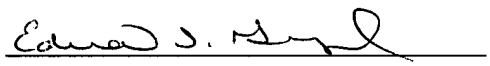
Applicants have provided arguments demonstrating that Silver et al. does not constitute prior art, and refuting the relevancy of the other primary references, namely Mackins I, Mackins II, Levi et al., Imamura et al. and Leurs et al. The secondary references cited by the examiner, namely the information in paragraph [0029] of the specification and the Avery reference, were cited with regards to the dependent claims, *inter alia*, claims 4, 5, 6, 7, 22, 23, 24 and 25. These secondary references were not cited against claim 1. As explained above, claim 1 is patentable over the cited art. The claims that depend on claim 1 are patentable at least for the same reasons claim 1 is patentable.

Accordingly, applicants respectfully request that the rejection of claims 1-30 under 35 U.S.C. §103(a) be withdrawn.

In view of the above amendments and remarks, applicants respectfully request reconsideration of the claims. Allowance of pending claims 1-30 is earnestly requested.

If the examiner has any questions regarding this amendment, the examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,



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